## *Remarks*

Reconsideration of this Application is respectfully requested.

### *I. Status of the Claims*

Upon entry of the foregoing amendment, claims 1, 4-8, 11-15, 18-21 and 55 are pending in the application, with 1, 5, 8, 15 and 55 being the independent claims. Claims 2, 3, 9, 10, 16 and 17 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 22-54 were previously cancelled without prejudice to or disclaimer of the subject matter therein. Claims 1, 8 and 15 are sought to be amended. New claim 55 is sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

### *II. The Amendment*

Claims 1, 8 and 15 have been amended to more particularly point out what Applicants regard as the invention. Claims 1, 8 and 15, as amended, specify that the translocating domain is a translocating domain of a bacterial or viral protein. Support for the amendment to claims 1, 8 and 15 can be found, *inter alia*, in claims 3, 10 and 17 as originally filed. New claim 55 specifies that the translocating domain is a translocating domain of a bacterial toxin, or a translocating domain of a virally expressed membrane

fusion protein. Support for new claim 55 can be found, *inter alia*, at page 7 of the specification, paragraph [0025], and in claims 1 and 4, as originally filed. Accordingly, no new matter has been added by the foregoing amendment.

### *III. The Withdrawal of the Previous Objections and Rejections*

Applicants wish to thank the Examiner for withdrawing the objection to claims 5, 12 and 19, and the rejection of claims 1-4, 6-11, 13-18, 20 and 21 under the judicially created doctrine of obviousness-type double patenting, set forth in the previous Office Action.

### *IV. The Rejection Under 35 U.S.C. § 112*

At pages 2-3 of the Office Action, the Examiner has maintained the rejection of claims 1-21 under 35 U.S.C. § 112, first paragraph, because the specification allegedly

> . . . does not reasonably provide enablement for a method of treating hypersecretion of mucus, asthma and COPD, administering [sic] topically to the airways of a patient in need thereof, a compound comprising a light chain (L-chain) or L-chain fragment of a clostridial neurotoxin containing the active proteolytic enzyme domain, a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion, and a translocating domain that translocates the L-chain or L-chain fragment into the target cell, with the proviso that the compound is not a botulinum toxin, *wherein the translocating domain is not identified or defined.*

Office Action, page 3 (emphasis added).

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claims 1, 8 and 15 to specify that the translocating domain is a translocating domain of a bacterial or viral protein. Moreover, claim 5 was previously amended to specify that the translocating domain is a translocating domain of

clostridial neurotoxin, diphtheria toxin, domain II of pseudomonas exotoxin A, influenza virus haemagglutinin, a fusogenic protein of Semliki Forest virus, vesicular stomatitis virus glycoprotein G, SER virus F protein or Foamy virus envelope glycoprotein. With regard to claim 5, the Examiner had previously recognized that the recited translocating domains are fully enabled by the specification. *See* page 3, lines 6-14, of the Office Action dated April 29, 2005. Additionally, new claim 55 defines the translocating domain as a translocating domain of a bacterial toxin, or a translocating domain of a virally expressed membrane fusion protein. Thus, the translocating domain is fully identified and defined in the claims of the present application.

Moreover, the claims of the present application are directed to methods of treating hypersecretion of mucus, chronic obstructive pulmonary disease or asthma comprising administering to a patient a compound having a translocating domain that translocates the L-chain or L-chain fragment into the target cell. Translocating domains suitable for use in the agents of the present invention have a common function in that they deliver the L-chain or L-chain fragment into the cell by a process of endocytosis. *See* Applicants' specification, page 9, paragraph 0030. In this regard, the only functional requirement of a translocation domain of the present invention is that it is capable of releasing the L-chain or L-chain fragment from the endosome by a process known as "endocytic release" by the skilled artisan.

As detailed in the present specification, suitable translocation domains may be obtained from a wide range of sources, in particular, microbial sources such as bacterial or viral sources. *See* Applicants' specification, page 7, paragraphs 0023-0024. A translocating domain can be an enzyme, such as a bacterial or viral toxin, which includes

the translocating domain of clostridial neurotoxin or diphtheria toxin, or domain II of pseudomonas exotoxin.

Alternatively, as described in the present specification, the translocating activity of the presently claimed agents may be derived from a virally expressed membrane fusion protein. Examples of such suitable proteins include influenza virus haemagglutinin, Semliki Forest virus fusogenic protein, vesicular stomatitis virus glycoprotein G, SER virus F protein and Foamy virus envelope glycoprotein. *See* Applicants' specification, page 7, paragraph 0025. Virally encoded "spike proteins" such as the E1 protein of SFV and the G protein of VSV can also provide the requisite translocating activity. *Id.*

The artisan skilled in the art, reading the present specification, would be able to identify suitable translocating domains for use in the present invention as a routine matter. By way of example, suitable methodologies are described in Applicants' specification at pages 7-9, paragraphs 0027 to 0030. In particular, Shone, C. C. *et al., Eur. J. Biochem. 167:* 175-180 (1987) and Blaustein, R. O. *et al., FEBS Letters 226*: 115-120 (1987), (cited as documents AT5 and AR4 respectively in Applicants' First Supplemental Information Disclosure Statement), provide simple assays to identify bacterial translocating domains having the desired translocating activity without undue experimentation. *See* Applicants' specification, page 9, paragraph 0030.

Applicants provide herewith a Declaration by Dr. Keith Foster (Exhibit A) stating that microbial or viral translocating domains for use in the present invention can be routinely identified by the artisan skilled in the art.

Applicants respectfully submit that for all the reasons stated above, and contrary to the Examiner's contention, the specification is fully enabled for the invention as claimed. In addition, the claims have been amended so that the translocating domain is fully described and identified. In view of the amendment and remarks stated above, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

At pages 3-7 of the Office Action, the Examiner has maintained the rejection of claims 1-21 under 35 U.S.C. § 112, first paragraph, because the specification allegedly

> . . . only discloses cursory conclusions (pages 2-3) without data supporting the findings, which state that a compound comprising an inhibiting domain comprising a light chain of a clostridial neurotoxin or a [sic] active fragment or variant thereof, a tranlocating domain that translocates the inhibiting domain into the cell, and a targeting domain that binds to a target cell of a mucus secreting cell or a neuronal cell controlling or directing mucus secretion, can be used to treat hypersecretion of mucus, asthma and COPD. *There are no indicia that the present application enables the full scope in view of the use of a compound comprising the inhibiting domain, the targeting domain and the translocating domain in treating hypersecretion of mucus, asthma and COPD* as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is encompassed.

Office Action, pages 3-4 (emphasis added). Further, according to the Examiner, "the specification has only demonstrated the in vitro effect of WGA-LHN/A (Example 3), it has not demonstrated the make/use of compounds containing various translocating domains in treating hypersecretion of mucus, COPD and asthma.", and "the specification has not demonstrated the use of the compounds containing various translocating domains in the treatment, it requires undue experimentation to assess their effects in treating hypersecretion of mucus, COPD and asthma." Office Action, page 8.

Applicants respectfully traverse the rejection.

First and foremost, as stated above, the specification at pages 7-9 provides a detailed description of how to obtain and identify microbial or viral translocating domains for use in the present invention. Thus, one of ordinary skill in the art, reading the present specification, would be able to make therapeutic compounds comprising the translocating domains of the present invention, without undue burden.

Second, Example 3 of the present specification describes the inhibition of neurotransmitter release from cultured neuronal cells by a particular conjugate of the present invention, namely WGA-LHN/A. This conjugate comprises a targeting domain derived from wheat germ agglutinin (WGA) and a translocating domain derived from botulinum toxin (BoNT) serotype A. Figures 4-6 in the specification clearly show the inhibiting effect of the WGA-LHN/A conjugate on neurotransmitter release.

Third, the presence of additional working examples in the specification is not required for enablement of the invention. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski, 164 U.S.P.Q. 642, 645 (CCPA 1970).* The present specification provides sufficient disclosure for one of skill in the art to carry out the invention without undue experimentation.

Applicants further provide the following experimental evidence to show that the compounds of the present invention have therapeutic activity. Three new conjugates prepared in accordance with the present invention were tested for their ability to inhibit mucin release. The first conjugate, LHN/C-EGF, has a translocating domain derived from botulinum toxin (BoNT) serotype C, which is structurally distinct from the botulinum

toxin (BoNT) serotype A of the WGA-LHN/A exemplified in the specification, and a targeting domain derived from epidermal growth factor (EGF). The second conjugate, LHN/B-EGF, has a translocation domain derived from BoNT serotype B, which is structurally distinct from the translocating domains derived from BoNT serotype A and from BoNT serotype C, and a targeting domain derived from epidermal growth factor (EGF). The third conjugate, LC/C-RGD-HN/C, has a translocation domain derived from BoNT serotype B and a targeting domain derived from Integrin, which binds to the Integrin receptor on target cells. Applicants measured the amount of released mucus in cell culture medium and cell mucin content after incubation of secreting cells with each conjugate, to determine the effect of the three different conjugates on mucin secretion from target cells. The data, provided in the enclosed Annex 1 (Exhibit B) and Figures 1-6 (Exhibit C), illustrate the results obtained using these three conjugates of the invention — namely, a concentration-dependent inhibition of mucus release from two different cell lines following treatment. These results confirm that conjugates of the present invention correctly translocate into the target cells and block secretion of mucin from the cells and thus would be useful in the presently claimed methods of treating hypersecretion of mucus, COPD and asthma.

Thus, a representative sample of the conjugates of the invention has been demonstrated to have therapeutic activity when tested in an art-accepted model of mucus secretion. Therefore, the artisan skilled in the art, reading the present specification, would be able to make and use the compounds comprising the translocating domains of the invention, without undue burden.

Applicants respectfully assert that for all the reasons stated above the claims of the present application are fully enabled by the specification and the additional experimental evidence provided herewith. Accordingly, the rejection of claims 1-21 under 35 U.S.C. § 112, first paragraph is improper. It is therefore respectfully requested that the rejection of claims 1-21 under 35 U.S.C. § 112, first paragraph be withdrawn.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

John M. Covert for Timothy J. Shea, Jr. Reg No. 38,759
Attorney for Applicants
Registration No. 41,306

Date: Feb. 21, 2006

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
424415_1.DOC